EXHIBIT D

LUNG CANCER

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Pathology of Lung Cancer: An Exercise in Classification

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INTRODUCTION

Unlike many other cancers, the incidence of lung cancer is increasing. In the United States it has become the leading cause of cancer deaths for both men and women. For 1993, 170,000 new cases and 149,000 deaths due to lung cancer were predicted.[13] Due to the poor results of current treatment, future efforts need to be directed to prevention, new methods for early detection, and new treatment strategies. A good understanding of the dynamics of lung cancer pathology and classification is necessary for devising plans to achieve these goals.

Most cancers of the lung are epithelial tumors, or carcinomas. Sarcomas and lymphomas of the lung are very rare.[69] In contrast to other common cancers, such as cancers of the colon, breast, and prostate, which are mostly adenocarcinomas, there are four histological types of lung cancers, each with distinct biological characteristics: small-cell carcinoma (SCLC), squamous-cell carcinoma, adenocarcinoma, and large-cell carcinoma.[5] Clinically and therapeutically, lung cancer is divided into SCLC and nonsmall-cell lung cancer (NSCLC). For SCLC, which is a neuroendocrine (NE) tumor comprising 20% of all cases, combination chemotherapy forms the cornerstone of therapy. The vast majority of patients respond to therapy with prolonged survival; there are a small percentage of cures. For NSCLC (squamous-cell carcinoma, adenocarcinoma, and large-cell carcinoma), surgery is the major curative modality for patients without demonstrable metastatic disease.

The main purpose of this chapter is to illustrate the broad spectrum of lung carcinomas. We will discuss histogenesis, tumor classification, and principles and applications of markers. Heterogeneity and interrelationships of various tumors will be noted. We will then review the major histologic types of lung cancers. We will also present the history of and current views on subtyping of SCLC, which is the most common NE tumor in the lung. In the "Other Neuroendocrine Tumors" section we will present carcinoid tumors and a newer entity, NSCLC with NE features, as well as review the nomenclature, classification, and clinicopathologic spectrum of NE differentiation. We have focused on NE lung tumors because it is an area where the results of tumor biology research are actively incorporated into classic histopathology to form relevant clinicopathologic entities. Finally, premalignant lesions of lung cancers will be reviewed in the light of changing histopathology. Recommended further reading that will complement this chapter includes Matthews and Linnoila,[65] and Marchevsky.[62]

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